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Chlorhexidine versus routine bathing to prevent multidrug-resistant organisms and all-cause bloodstream infections in general medical and surgical units (ABATE Infection trial): a cluster-randomised trial

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Summary

Background
Universal skin and nasal decolonisation reduces multidrug-resistant pathogens and bloodstream infections in intensive care units. The effect of universal decolonisation on pathogens and infections in non-criticalcare units is unknown. The aim of the ABATE Infection trial was to evaluate the use of chlorhexidine bathing in noncritical-care units, with an intervention similar to one that was found to reduce multidrug-resistant organisms and bacteraemia in intensive care units.

Methods
The ABATE Infection (active bathing to eliminate infection) trial was a cluster-randomised trial of 53 hospitals comparing routine bathing to decolonisation with universal chlorhexidine and targeted nasal mupirocin in non-critical-care units. The trial was done in hospitals affiliated with HCA Healthcare and consisted of a 12-month baseline period from March 1, 2013, to Feb 28, 2014, a 2-month phase-in period from April 1, 2014, to May 31, 2014, and a 21-month intervention period from June 1, 2014, to Feb 29, 2016. Hospitals were randomised and their participating non-critical-care units assigned to either routine care or daily chlorhexidine bathing for all patients plus mupirocin for known methicillin-resistant Staphylococcus aureus (MRSA) carriers. The primary outcome was MRSA or vancomycin-resistant enterococcus clinical cultures attributed to participating units, measured in the unadjusted, intention-to-treat population as the HR for the intervention period versus the baseline period in the decolonisation group versus the HR in the routine care group. Proportional hazards models assessed differences in outcome reductions across groups, accounting for clustering within hospitals. This trial is registered with ClinicalTrials.gov, number NCT02063867.

Findings
There were 189 081 patients in the baseline period and 339 902 patients (156 889 patients in the routine care group and 183 013 patients in the decolonisation group) in the intervention period across 194 non-critical-care units in 53 hospitals. For the primary outcome of unit-attributable MRSA-positive or VRE-positive clinical cultures (figure 2), the HR for the intervention period versus the baseline period was 0·79 (0·73–0·87) in the

decolonization group versus 0·87 (95% CI 0·79–0·95) in the routine care group. No difference was seen in the relative HRs (p=0·17). There were 25 (<1%) adverse events, all involving chlorhexidine, among 183 013 patients in units assigned to chlorhexidine, and none were reported for mupirocin.

Interpretation
Decolonisation with universal chlorhexidine bathing and targeted mupirocin for MRSA carriers did not significantly reduce multidrug-resistant organisms in non-critical-care patients.

Funding
National Institutes of Health.

Research in context

Evidence before this study

Several cluster-randomised trials in intensive care units (ICUs) have led to the widespread adoption of universal ICU decolonisation involving daily chlorhexidine bathing with or without nasal ointments to prevent bloodstream infections and methicillin-resistant Staphylococcus aureus (MRSA).These trials have also led to national guidance in the USA for the use of daily chlorhexidine bathing in ICUs to reduce device-associated infections, specifically central line-associated bloodstream infections.Only modest experimental evidence has been gathered about the effect of universal decolonisation in non-ICU settings. We searched PubMed for “chlorhexidine bathing” (MeSH Terms) and “hospital,” excluding “intensive care unit”, or “ICU” and found four quasi-experimental studies. One study found a 64% reduction in hospital-associated MRSA and vancomycin-resistant enterococcus (VRE) infections compared with historical controls after 14 months of daily bathing with chlorhexidine in four general medical units at an academic centre. Another study found a 55% reduction in hospitalassociated MRSA and a 36% reduction in hospital-associated VRE after chlorhexidine bathing for 7 months in a crossover study of four general medical units at an academic centre. A third study with a non-randomised, stepped-wedge design involving 19 months of hospital-wide chlorhexidine bathing reported a 29% reduction in Clostridium difficile infection with thrice weekly chlorhexidine bathing, and a 59% reduction in C difficile infection with daily chlorhexidine bathing. In the last study, one chronic care hospital unit was randomly assigned to bathe patients daily with chlorhexidine for 12 months resulting in a 71% reduction in MRSA incidence among 122 patients, although the reported benefit was not significant. All but one study used 2% no-rinse chlorhexidine cloths. Reported adherence with chlorhexidine bathing in these studies was approximately 60%.

Added value of this study

The ABATE Infection (active bathing to eliminate infection) trial is the first large-scale cluster-randomised trial to evaluate whether universal chlorhexidine bathing for all patients plus mupirocin for MRSA carriers in non-critical-care units reduces multidrug-resistant organisms and all-cause bloodstream infection. Chlorhexidine compliance was higher than in the four quasi-experimental studies reported above. We found that universal decolonisation did not reduce infection in the overall population, but in post-hoc analyses of patients with medical devices the regimen was associated with significant reductions in all-cause bloodstream infections and MRSA or VRE clinical cultures.

Implications of all the available evidence

Although previous single-centre, quasi-experimental studies in non-ICU settings found broad infection reduction benefits with daily chlorhexidine use in patients in academic hospitals, the ABATE Infection trial did not find significant benefits in non-critical-care patients. Our results contrast with those showing benefits of universal decolonisation over routine care in several trials of ICUs. Current US ICU guidance to use daily chlorhexidine bathing for prevention of central line-associated infections has led many hospitals to adopt daily chlorhexidine bathing for all patients with central lines and other devices, although evidence in non-ICU patients has been lacking. The post-hoc analysis in the ABATE Infection trial found that non-ICU patients with medical devices had a significant 37% reduction in MRSA and VRE and a significant 31% reduction in all-cause bloodstream infections. Patients with medical devices constituted only 10% of the inpatient population, but were responsible for 37% of MRSA and VRE cultures and 56% of all-cause bloodstream infections. Despite these findings, further research is needed to confirm these effects if the decolonisation strategy is applied only to patients with medical devices, since the ABATE Infection trial involved universal decolonisation in all patients.

Introduction

Extensive reductions in health-care-associated infections have been achieved in the USA, largely because of successful infection prevention efforts in intensive care units (ICUs).[1] Investments in infection reduction have led to several multicentre trials of infection prevention strategies in ICUs.[2–13] Notably, several recent trials of universal decolonisation involving daily chlorhexidine bathing with and without nasal mupirocin prompted widespread adoption of this practice in ICUs, because of evidence that universal decolonisation reduces device-associated bacteraemia, all-cause bacteraemia, and multidrug-resistant organisms.[7–13]

Although the patient-specific risk is highest in ICUs, most health-care-associated infections occur outside the ICU, because the patient populations are so much larger.

Questions remain about the use of ICU-proven strategies across entire hospitals, because they could potentially have a higher cost-to-benefit ratio and lower overall effect on infection prevention.

We aimed to evaluate the use of chlorhexidine bathing in non-critical-care units, with an intervention similar to one that was found to reduce multidrug-resistant organisms and bacteraemia in ICUs.[7]

Methods

Study design and participants

The ABATE Infection (active bathing to eliminate infection) trial was a cluster-randomised trial of 53 hospitals comparing routine bathing to decolonisation with universal chlorhexidine and targeted nasal mupirocin in non-critical-care units. Central institutional review board (IRB) approval was obtained from Harvard Pilgrim Health Care (Boston, MA, USA) with a waiver of informed consent. All participating hospitals formally ceded IRB oversight to the Harvard Pilgrim Health Care IRB, except for the designated IRB at Chippenham and Johnston Willis Hospitals that provided prisoner oversight for the trial.

The trial consisted of a 12-month baseline period from March 1, 2013, to Feb 28, 2014, a 2-month phase-in period from April 1, 2014, to May 31, 2014, and a 21-month intervention period from June 1, 2014, to Feb 29, 2016. Recruitment occurred among hospitals affiliated with HCA Healthcare (HCA) with the goal of obtaining 50 participating hospitals. HCA hospitals account for 5% of US hospitalisations and nearly all are community hospitals. Eligibility criteria included hospitals with adult non-critical-care units, including medical, surgical, mixed medical and surgical, oncology, and step-down units. Bone marrow transplant, peripartum care, psychiatry, paediatric, and acute rehabilitation units were excluded from being study units within participating hospitals. Units were also excluded if they had initiated an intervention that conflicted with the trial (eg, universal decolonisation), had a mean length of stay of less than 2 days, or had more than 30% of patients undergoing cardiac or orthopaedic surgery, because of the high use of nasal mupirocin in these patient populations. Participating hospitals were required to have stable infection prevention initiatives during the baseline period, and agreed to refrain from new infection prevention initiatives conflicting with the trial.

Randomisation and masking

Hospitals were randomly assigned either to routine care or to decolonisation. Randomisation occurred at the end of the baseline period (November, 2013) so that hospitals would know their group assignment and would adopt any trial interventions during the phase-in and intervention periods. The first four months of baseline data were used to establish similar hospital pairs based on key variables representing aggregated data from participating units at each hospital. These key variables included annual hospital admissions, unit-attributable patient days, percentage of surgical patients, percentage of cardiac and orthopaedic surgery patients, prevalence of methicillinresistant

Staphylococcus aureus (MRSA) or vancomycinresistant enterococcus (VRE), Romano comorbidity score,[14] and rates of MRSA and VRE clinical cultures and all-pathogen bloodstream infections (per 1000 unitattributable days). Pairing was done by calculating the Mahalanobis distance between facilities across baseline values of equally-weighted key variables and choosing pairings with the minimum average within-pair distance.[15] A single pseudo-random number uniformly distributed between 0 and 1 was generated for each pair. If the number was less than 0·5, the arbitrary first member of the pair was assigned to routine care and the other to decolonisation. If the number was at least 0·5, then the assignments were reversed. The remaining unpaired hospital of 53 participants was assigned as the arbitrary first member of a pair with no match.

Procedures

The unit of randomisation was the hospital, with all participating units in each hospital assigned to the same group. Non-critical-care units following routine care continued to use their routine non-antiseptic disposable cloths for bed bathing, and liquid soap for showering at their usual frequency. This group was considered standard of care (see routine care protocol in appendix). Non-critical-care units following the decolonization procedure had routine soap exchanged for 4% rinse-off liquid chlorhexidine in the shower and 2% leave-on chlorhexidine disposable cloths for bed baths. Daily bathing or showering was encouraged. Post-showering application of 2% leave-on chlorhexidine to wounds and devices was included as part of protocol training. Additionally, patients known to the hospital to be MRSA carriers (by reported history, previous culture results, or information from transferring facilities) received twice-daily nasal 2% mupirocin ointment for five days while on a participating unit, because the combination of mupirocin plus chlorhexidine has been shown to effectively reduce colonisation and infection caused by MRSA (see decolonisation protocol in appendix).[7,16,17] On-site implementation of the decolonisation procedure was done by hospital personnel responsible for local quality improvement processes, including infection prevention personnel and unit managers and directors. Usual communication channels and implementation methods for quality improvement initiatives were used, including computer-based training, daily electronic charting of bathing compliance in routine nursing documentation systems, and charting of each mupirocin administration in medication records. Hospitals in the decolonisation group received educational materials for staff and patients, static-cling posters for each patient's room to encourage daily baths, and waterproof step-bystep instructions in every shower. On-site training was provided for use of 2% chlorhexidine-impregnated cloths, with emphasis on comprehensive bathing, including cleansing of superficial wounds and devices within six inches of the body. In addition to the daily charting of bathing compliance, nursing leaders of participating units observed three chlorhexidine bed baths every 3 months and obtained three patient self-assessments on bathing using a checklist provided by investigators to visually assess protocol adherence. These skills assessments were used to tailor further unit training on the protocol. All skin and prophylactic (non-treatment) wound products were confirmed to be chlorhexidine compatible, and adverse events were managed by treating physicians. Investigators held monthly coaching calls for intervention and control groups to discuss implementation, protocol adherence, and verify

that new initiatives were disclosed for assessment of trial conflict. Hospital study champions from both groups received feedback reports to encourage adherence (avoidance of decolonisation for the routine care group and adherence to decolonisation for the decolonisation group). The groups also received reminders to document bathing, feedback for missed nursing documentation, and presentations that reviewed national best practice for infection prevention.

Outcomes

The primary outcome was combined MRSA or VRE clinical cultures attributable to a participating unit. Unitattributable days were defined as days occurring from 3 days into the unit stay through 2 days after unit discharge if the patient was still hospitalised. Cultures from any body site were included with the exception of screening cultures, such as nasal surveillance cultures for MRSA or rectal surveillance cultures for VRE. The two secondary outcomes were clinical cultures of multidrug-resistant Gram-negative rods (GNR) and all-pathogen bloodstream infection attributable to a participating unit. Multidrugresistant GNR were defined as follows: extended-spectrum β-lactamase producers; carbapenem-resistant Enterobacteriaceae; acinetobacter species resistant to all third and fourth generation cephalosporins plus extendedspectrum penicillins with β-lactamase inhibitors; and pseudomonas species resistant to aztreonam, all third and fourth generation anti-pseudomonal cephalosporins, and extended-spectrum penicillins with β-lactamase inhibitors. Consistent with planned analyses, only the first event per patient was assessed for each outcome.

Additional prespecified outcomes for secondary exploratory studies include urinary tract infections, Clostridium difficile infections, blood culture contamination, 30-day infectious readmissions, resistance to chlorhexidine or mupirocin, and cost-effectiveness. These analyses will be reported elsewhere.

We did post-hoc analyses of four subgroups for each outcome assessed. First, we did post-hoc analyses of both the primary and bloodstream infection outcomes for two subgroups: patients with devices, including central venous catheters (and accessed ports), midline catheters, and lumbar drains; and patients in dedicated oncology units. Next, we did post-hoc analyses of subgroups for selected outcomes. We assessed whether the subset of participating hospitals with the highest baseline rate of MRSA and VRE clinical cultures (per 1000 unit-attributable days) experienced a change in that specific outcome because of the intervention. Similarly, we assessed whether the subset of participating hospitals with the highest baseline rate of all-pathogen bloodstream infections (per 1000 unitattributable days) experienced a change in that specific outcome because of the intervention. Finally, we did posthoc analyses in patients with a history of MRSA to assess MRSA clinical cultures alone in addition to bloodstream infection outcomes, since those patients received mupirocin in addition to chlorhexidine according to the trial protocol.

Census, microbiology, pharmacy, supply chain, nursing documentation, and administrative data were obtained from the HCA centralised clinical data warehouse. For microbiological outcomes, pathogens were attributed to a participating unit if the collection date occurred more than 2 days after unit admission through 2 days after unit

discharge, consistent with US Centers for Disease Control and Prevention (CDC) guidance18 for surveillance of hospital-associated infections. Skin commensals in blood cultures were only considered bloodstream infections if CDC criteria were met.[19]

Site-specific champions at decolonisation hospitals were asked to report any adverse events to study staff. Reminders were given on monthly coaching calls

Statistical analysis

We powered the trial on the rarest outcome, all-pathogen bloodstream infection. With 53 hospitals and 21 months of follow-up, we had 89% power to detect a two-tailed 20% difference in the decolonisation group versus the routine care group. 1 year into the intervention period, the trial was elongated from 18 months to 21 months following a reassessment of power. The reassessment of power involved analysis of the full 12 months of baseline data, whereas the initial assessment had only involved analysis of 4 months of baseline data.[20] No data from the intervention period was accessed during this reassessment.

All outcomes were assessed by unadjusted, intention-to-treat analyses using proportional hazard models with shared frailties to account for clustering within hospitals.[21,22] For each outcome, the trial's effect was measured by the significance of the group-by-treatment period interaction, which assessed whether the hazard ratio (HR) between intervention versus baseline periods differed significantly between study groups. As a conservative approach, we ignored the pair matching we did during randomisation.[23] Data from the 2-month phase-in period were excluded from all analyses.

We did additional adjusted and as-treated analyses. Adjusted models accounted for individual age, gender, race, history of multi-drug resistant organisms, Medicaid insurance, previous nursing home stay within 90 days of admission, Romano comorbidity score, unit type (medical, surgical, mixed medical-surgical, oncology, and step-down), transplant hospitals, and surgery during admission. Regarding multi-drug resistant organism history, the outcome of MRSA and VRE clinical cultures was adjusted for history of MRSA and VRE; the outcome of multidrug-resistant GNR clinical cultures was adjusted for history of multidrug-resistant GNR; and the outcome of all-pathogen bloodstream infections was adjusted for history of MRSA, VRE, and multidrugresistant GNR.

For the post-hoc analyses of four subgroups for two outcomes (the primary and bloodstream infection outcomes), we accounted for multiple comparisons by using a Bonferroni correction with an α-level of 0·00625 (p=0·05 divided by 8). If a test of MRSA or VRE clinical cultures was significant using this standard, we assessed MRSA and VRE clinical cultures separately using an α-level of 0·025 (p=0·05 divided by 2).

All analyses were done with SAS 9.3 (SAS Institute, Cary, NC, USA). This trial is registered with ClinicalTrials. gov, number NCT02063867.

Role of the funding source

Companies contributing product or federal agencies providing grant funds had no role in study design, data collection, data analysis, data interpretation, or writing of the

report. The corresponding author (SSH), programmer analyst (TRA), and statistician (KK) had full access to all the data in the study and all authors were responsible for the decision to submit for publication.

Results

158 hospitals in 14 US states were invited to participate, and 53 were enrolled and randomised. Collectively, participating hospitals had 194 non-critical-care units (64 medical, 26 surgical, 72 mixed medical-surgical, seven oncology, and 25 step-down units).

Five hospitals withdrew after the intervention period started: two hospitals in the routine care group because of competing interventions, and three hospitals in the decolonisation group because of a competing intervention, closure of the only participating unit, and hospital divestiture from HCA (figure 1). With the exception of HCA divestiture, hospital data were available from the HCA centralised clinical data warehouse for the entirety of the baseline and intervention periods, regardless of withdrawal from the trial.

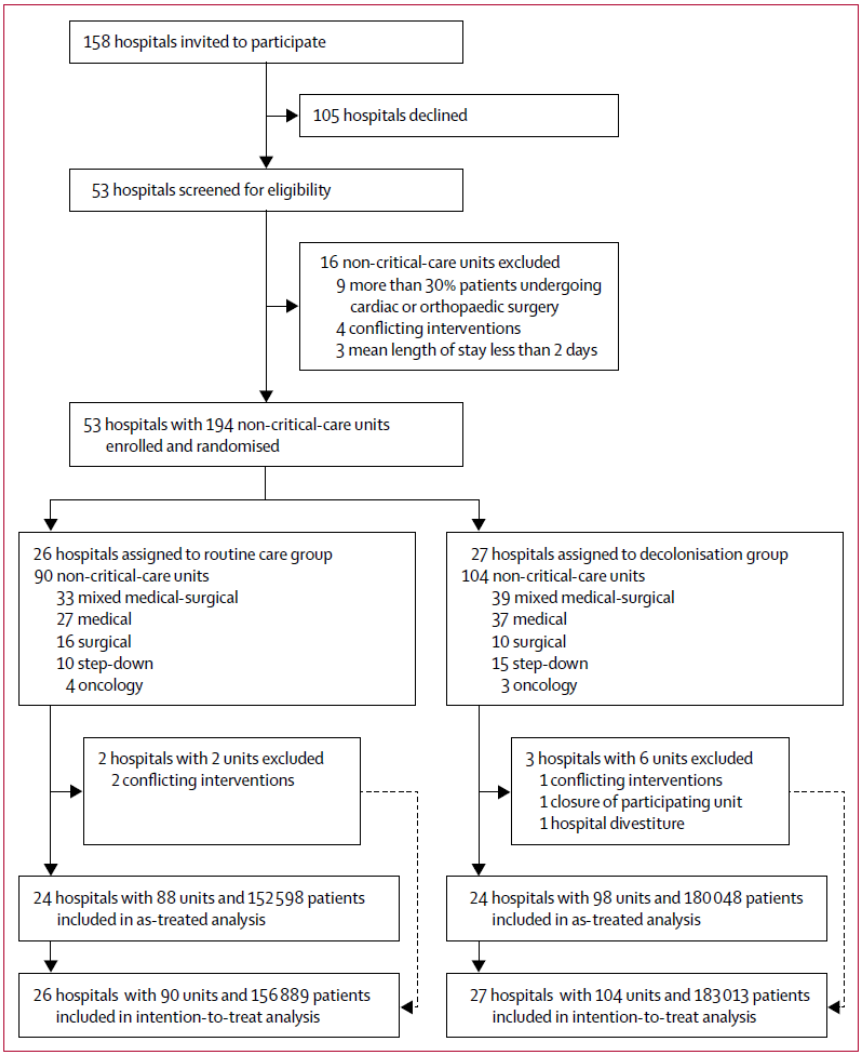

Figure 1: Trial profile for the intervention period

There were 189 081 patients in the baseline period and 339 902 patients (156 889 patients in the routine care group and 183 013 patients in the decolonisation group) in the intervention period. Patient characteristics were highly similar across groups (table 1; see appendix for the distribution of medical device types across groups). In the decolonisation group, median compliance with chlorhexidine bathing or showering across participating hospitals was 79% (IQR 66%–79%), reflecting a median number of 28 184 (IQR 22 734–37 479) bathing assessments as routinely documented in the medical record. Among those who used chlorhexidine, sampling across hospitals found 7669 (78%) of 9843 patients had bed baths versus showers. Median compliance with mupirocin in the decolonisation group was 88% (IQR 81%–91%), reflecting a median number of 1803 (IQR 1166–2639) assessments among MRSA carriers in participating hospitals. In the routine care group, chlorhexidine use for bathing or showering was rare across participating hospitals (median 1%, IQR 0–2%), reflecting a median of 12 325 (IQR 8166–18 408) assessments. Use of mupirocin among MRSA carriers was similarly rare (median 1%, IQR 0–3%) and was usually for pre-operative purposes, reflecting a median of 785 assessments (IQR 410–1019).

	Patients in baseline period (n=189 081)		Patients in intervention period (n=339 902)	
	Routine care	Decolonisation	Routine care	Decolonisation
Hospital admissions	87 277 (100%)	101 804 (100%)	156 889 (100%)	183 013 (100%)
Unit-attributable patient days	320 938	382 932	597 762	714 598
Hospital stay (days)	5 (4–7)	5 (4–8)	5 (4–8)	5 (4–8)
Participating unit stay (days)	4 (3–6)	4 (3–7)	4 (3–6)	4 (3–7)
Age (years)	62·6 (18·2)	62·9 (18·4)	62·3 (18·2)	62·6 (18·6)
Sex*				
Female	47 224 (54·1%)	55 741 (54·8%)	84 585 (53·9%)	100 249 (54·8%)
Male	40 048 (45·9%)	46 057 (45·2%)	72 288 (46·1%)	82 748 (45·2%)
Race				
White	61 244 (70·2%)	65 108 (64·0%)	107 261 (68·4%)	112 067 (61·2%)
Hispanic	10 813 (12·4%)	19 332 (19·0%)	22 581 (14·4%)	38 704 (21·1%)
Black	11 478 (13·2%)	11 899 (11·7%)	21 501 (13·7%)	22 462 (12·3%)
Asian	846 (1·0%)	1694 (1·7%)	2021 (1·3%)	4175 (2·3%)
Other or unknown	2896 (3·3%)	3771 (3·7%)	3525 (2·2%)	5605 (3·1%)
Insurance				
Medicare	49 817 (57·1%)	58 071 (57·0%)	88 055 (56·1%)	103 659 (56·6%)
Commercial	18 572 (21·3%)	24 048 (23·6%)	30 863 (19·7%)	39 797 (21·7%)
Medicaid	8059 (9·2%)	8035 (7·9%)	17 740 (11·3%)	17 010 (9·3%)
Other	10 743 (12·3%)	11 343 (11·1%)	16 720 (10·7%)	18 338 (10·0%)
Unknown	86 (0·1%)	307 (0·3%)	3511 (2·2%)	4209 (2·3%)
Comorbidities				
Diabetes	24 915 (28·5%)	30 167 (29·6%)	46 078 (29·4%)	55 468 (30·3%)
Chronic pulmonary disease	18 230 (20·9%)	18 383 (18·1%)	32 803 (20·9%)	32 482 (17·7%)
Anaemia	18 380 (21·1%)	23 333 (22·9%)	32 054 (20·4%)	41 056 (22·4%)
Renal failure	12 375 (14·2%)	14 803 (14·5%)	21 767 (13·9%)	26 989 (14·7%)
Obesity	12 189 (14·0%)	15 188 (14·9%)	21 679 (13·8%)	27 770 (15·2%)
Congestive heart failure	8005 (9·2%)	8489 (8·3%)	14 205 (9·1%)	15 346 (8·4%)
Peripheral vascular disease	5715 (6·5%)	7052 (6·9%)	9431 (6·0%)	11 532 (6·3%)
Liver disease	2842 (3·3%)	3757 (3·7%)	5052 (3·2%)	6591 (3·6%)
Rheumatic disease	2571 (2·9%)	3210 (3·2%)	4442 (2·8%)	5312 (2·9%)
Cancer	4087 (4·7%)	5367 (5·3%)	6925 (4·4%)	8967 (4·9%)
History of MRSA	1813 (2·1%)	1937 (1·9%)	2976 (1·9%)	2915 (1·6%)
History of VRE	595 (0·7%)	478 (0·5%)	891 (0·6%)	632 (0·3%)
History of multidrug-resistant GNR	1736 (2·0%)	2068 (2·0%)	3007 (1·9%)	3609 (2·0%)
Surgery during admission	18 427 (21·1%)	23 152 (22·7%)	32 736 (20·9%)	41 039 (22·4%)

(Table 1 continues on next page)

	Patients in baseline period (n=189 081)		Patients in intervention period (n=339 902)	
	Routine care	Decolonisation	Routine care	Decolonisation
(Continued from previous page)				
ICU stay before participating unit stay	7200 (8·2%)	7486 (7·4%)	12 693 (8·1%)	14 416 (7·9%)
SNF stay within 90 days before participating unit stay	1765 (2·0%)	2063 (2·0%)	3316 (2·1%)	3739 (2·0%)
Patients with medical devices	9578 (11·0%)	13 058 (12·8%)	15 372 (9·8%)	23 417 (12·8%)
Unit type				
Mixed medical-surgical	32 635 (37·4%)	38 191 (37·5%)	58 245 (37·1%)	69 835 (38·2%)
Medical	30 110 (34·5%)	38 464 (37·8%)	53 856 (34·3%)	69 158 (37·8%)
Surgery	14 172 (16·2%)	11 022 (10·8%)	26 418 (16·8%)	19 840 (10·8%)
Step-down	8713 (10·0%)	12 084 (11·9%)	15 294 (9·7%)	20 423 (11·2%)
Oncology	1647 (1·9%)	2043 (2·0%)	3076 (2·0%)	3757 (2·1%)

Data are n, n (%), median (IQR), or mean (SD). Data from the phase-in period were excluded from all analyses. The method of collection of race data changed between baseline and intervention periods. In the baseline period, respondents were asked to select one response from a list of race categories, which included Hispanic. In the intervention period, Hispanic ethnicity was asked separately from race and respondents were allowed to select up to two race categories. Age and comorbidity data not available for 16 patients. History of MRSA, VRE, and multidrug-resistant GNR of each patient was available from March 1, 2013. Pathogens were attributed to a participating unit if the collection date occurred more than 2 days after unit admission through 2 days after unit discharge. MRSA=methicillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococcus. GNR=Gram-negative rods. ICU=intensive care unit. SNF=skilled nursing facility. *Data not available for 43 patients.

Table 1: **Characteristics of the patient population**

For the primary outcome of unit-attributable MRSA-positive or VRE-positive clinical cultures (figure 2), the HR for the intervention period versus the baseline period was 0·79 (0·73–0·87) in the decolonisation group versus 0·87 (95% CI 0·79–0·95) in the routine care group. The difference in the relative HRs was not significant (p=0·17; table 2). The HRs of the secondary outcomes for the intervention period versus the baseline period were also not significantly different across study groups. For multidrug-resistant GNR clinical cultures, routine care HR was 0·81 (95% CI 0·72–0·91) and decolonisation HR was 0·91 (0·82–1·00; p=0·16); and for all-pathogen bloodstream infections routine care HR was 0·96 (0·85–1·08) and decolonisation HR was 0·90 (0·80–1·01; p=0·43; figure 2). Adjusted and as-treated results were similar (table 2). The number of outcome events per trial outcome and their associated rates per 1000 patient days at risk are shown in table 3.

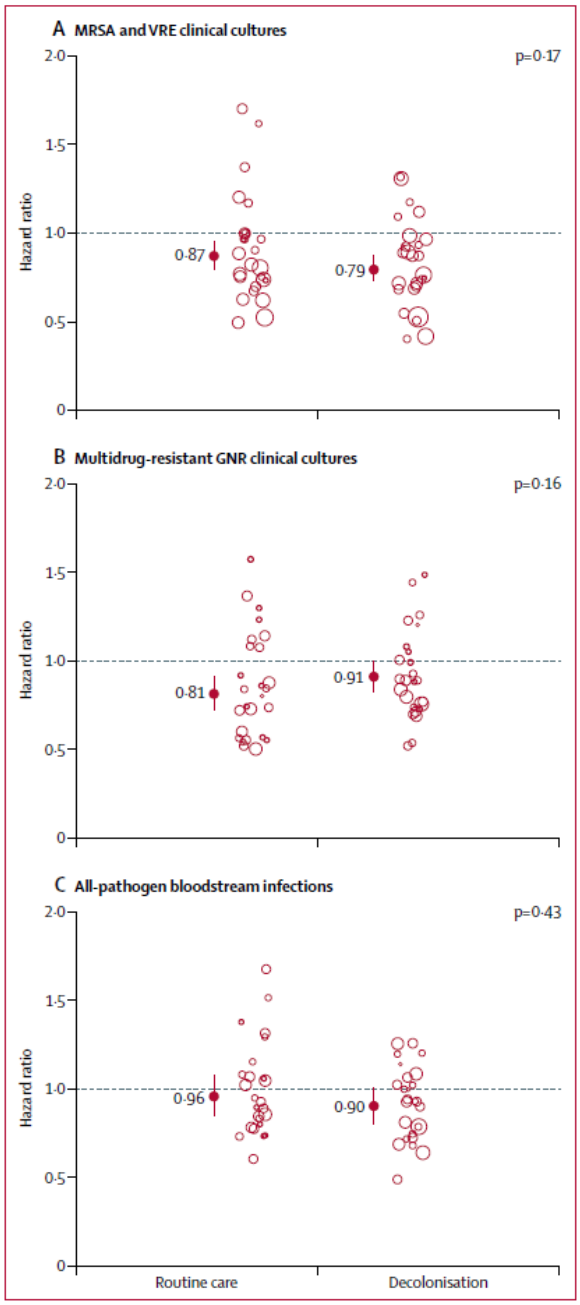

Figure 2: Outcomes in overall population

Effect of trial interventions on trial outcomes in the overall population (unadjusted, intention-to-treat). Group-specific hazard ratios and confidence intervals from proportional hazards models accounting for clustering by hospitals are shown for clinical cultures of MRSA or VRE (A), multidrug-resistant Gram-negative rods (B), and all-pathogen bloodstream infections (C). Bubble plots of hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown adjacent to group-specific hazard ratios and confidence intervals. The size of the bubble reflects the relative number of patients contributing data to the trial. GNR=Gram-negative rods.

	Routine care	Decolonisation	p value
Unadjusted intention-to-treat analysis	244166	284817	
MRSA or VRE clinical cultures	0·87 (0·79–0·95)	0·79 (0·73–0·87)	0·17
All-pathogen bloodstream infections	0·96 (0·85–1·08)	0·90 (0·80–1·01)	0·43
Multidrug-resistant GNR clinical cultures	0·81 (0·72–0·91)	0·91 (0·82–1·00)	0·16
Adjusted intention-to-treat analysis	244166	284817	..
MRSA or VRE clinical cultures	0·89 (0·81–0·97)	0·84 (0·76–0·91)	0·33
All-pathogen bloodstream infections	0·97 (0·86–1·09)	0·92 (0·82–1·03)	0·53
Multidrug-resistant GNR clinical cultures	0·85 (0·76–0·95)	0·93 (0·84–1·03)	0·27
Unadjusted as-treated analysis	239875	281696	..
MRSA or VRE clinical cultures	0·87 (0·80–0·96)	0·79 (0·72–0·86)	0·11
All-pathogen bloodstream infections	0·95 (0·84–1·08)	0·91 (0·81–1·01)	0·54
Multidrug-resistant GNR clinical cultures	0·82 (0·73–0·92)	0·91 (0·82–1·00)	0·18
Hospitals with highest quartile baseline rate of MRSA or VRA clinical cultures	65767	57550	..
MRSA or VRA clinical cultures	0·68 (0·57–0·79)	0·69 (0·59–0·82)	0·81
Hospitals with highest quartile baseline rate of all-pathogen bloodstream infections	10621	101661	..
All-pathogen bloodstream infections	0·86 (0·67–1·11)	0·81 (0·69–0·96)	..
Patients with medical devices	24950	36475	0·71
MRSA or VRE clinical cultures	1·17 (1·00–1·37)	0·80 (0·69–0·92)	0·0004*
MRSA clinical cultures only	1·17 (0·99–1·39)	0·87 (0·74–1·02)	0·0126*
VRE clinical cultures only	1·26 (0·85–1·86)	0·58 (0·44–0·78)	0·0020*
All-pathogen bloodstream infections	1·13 (0·96–1·33)	0·81 (0·70–0·94)	0·0032*
Patients in oncology units	4723	5800	..
MRSA or VRE clinical cultures	0·68 (0·33–1·40)	0·61 (0·31–1·20)	0·83
All-pathogen bloodstream infections	0·84 (0·42–1·66)	0·78 (0·36–1·70)	0·90
Patients with a history of MRSA	4789	4852	..
MRSA clinical cultures only	0·85 (0·74–0·98)	0·93 (0·80–1·07)	0·41
All-pathogen bloodstream infections	0·97 (0·71–1·32)	0·94 (0·70–1·26)	0·89

Data are n patients or HR (95% CI). Primary and secondary outcomes were assessed by measuring whether the hazard ratios during intervention versus baseline periods differed significantly between study groups using proportional hazards models accounting for clustering by hospital. MRSA=methicillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococcus. GNR=Gram-negative rods. *Remained significant after adjusting for multiple comparisons.

Table 2: **Hazard ratios for all trial outcomes, in total non-critical-care population and population subgroups**

	Routine care		Decolonisation	
	Baseline period	Intervention period	Baseline period	Intervention period
Unadjusted intention-to-treat analysis	87 277	156 889	101 804	183 013
MRSA or VRE clinical cultures	756/316 391 (2·39)	1209/588 916 (2·05)	838/376 808 (2·22)	1224/705 283 (1·74)
All-pathogen bloodstream infections	407/317 556 (1·28)	740/590 514 (1·25)	490/378 050 (1·30)	830/706 190 (1·18)
Multidrug-resistant GNR clinical cultures	481/316 988 (1·52)	741/591 934 (1·25)	584/377 832 (1·55)	1003/705 380 (1·42)
Adjusted intention-to-treat analysis	87 277	156 889	101 804	183 013
MRSA or VRE clinical cultures	756/316 391 (2·39)	1209/588 916 (2·05)	838/376 808 (2·22)	1224/705 283 (1·74)
All-pathogen bloodstream infections	407/317 556 (1·28)	740/590 514 (1·25)	490/378 050 (1·30)	830/706 190 (1·18)
Multidrug-resistant GNR clinical cultures	481/316 988 (1·52)	741/591 934 (1·25)	584/377 832 (1·55)	1003/705 380 (1·42)
Unadjusted as-treated analysis	87 277	152 598	101 648	180 048
MRSA or VRE clinical cultures	756/316 391 (2·39)	1184/573 476 (2·06)	836/376 275 (2·22)	1199/695 510 (1·72)
All-pathogen bloodstream infections	407/317 556 (1·28)	716/575 057 (1·25)	490/377 513 (1·30)	826/696 222 (1·19)
Multidrug-resistant GNR clinical cultures	481/316 988 (1·52)	729/576 367 (1·26)	584/377 295 (1·55)	993/695 403 (1·43)
Hospitals with highest quartile baseline rate of MRSA or VRA clinical cultures	23 903	41 864	21 346	36 204
MRSA or VRA clinical cultures	311/84 274 (3·69)	381/154 892 (2·46)	369/80 154 (3·36)	321/139 468 (2·30)
Hospitals with highest quartile baseline rate of all-pathogen bloodstream infections	14 476	26 145	35 760	65 907
All-pathogen bloodstream infections	95/49 367 (1·93)	162/96 407 (1·68)	225/129 850 (1·73)	340/240 660 (1·41)
Patients with medical devices	9578	15 372	13 058	23 417
MRSA or VRE clinical cultures	229/65 976 (3·47)	446/111 423 (4·00)	329/86 022 (3·82)	486/171 516 (2·83)
MRSA clinical cultures only	196/66 380 (2·95)	378/112 260 (3·37)	252/87 255 (2·89)	394/172 906 (2·28)
VRE clinical cultures only	37/67 601 (0·55)	81/115 055 (0·70)	85/88 291 (0·96)	101/175 450 (0·58)
All-pathogen bloodstream infections	218/65 833 (3·31)	413/111 070 (3·72)	311/86 056 (3·61)	494/170 840 (2·89)
Patients in oncology units	1647	3076	2043	3757
MRSA or VRE clinical cultures	13/6708 (1·94)	17/13 147 (1·29)	16/8405 (1·90)	17/14 743 (1·15)
All-pathogen bloodstream infections	13/6689 (1·94)	22/13 074 (1·68)	11/8404 (1·31)	15/14 717 (1·02)
Patients with a history of MRSA	1813	2976	1937	2915
MRSA clinical cultures only	319/7770 (41·06)	466/14 556 (32·01)	321/9116 (35·21)	451/14 544 (31·01)
All-pathogen bloodstream infections	66/9322 (7·08)	110/16 795 (6·55)	77/10 630 (7·24)	110/16 838 (6·53)

Data are n patients or n events/N unit-attributable days (n per 1000 unit-attributable days). Outcome events per trial were counted as events per at-risk days, and then measured per 1000 unit-attributable patient days. MRSA=methicillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococcus. GNR=Gram-negative rods.

Table 3: **Outcome events per unit-attributable days for all trial outcomes, in total non-critical-care population and population subgroups**

Post-hoc analyses were done to assess if a high risk subgroup would benefit from decolonisation when the overall non-ICU population did not (table 2). Patients with medical devices had a 32% greater reduction in allcause bacteraemia and a 37% greater reduction in MRSA or VRE clinical cultures compared with the routine care group. When evaluating MRSA alone and VRE alone, there was a 30% reduction in MRSA clinical cultures and a 67% reduction in VRE clinical cultures compared with the routine care group (figure 3). These findings remained significant after accounting for multiple comparisons (table 2). Patients who had medical devices accounted for 15 372 (10%) of 156 889 patients of the routine care intervention period population, but had 446 (37%) of 1209 of MRSA or VRE cultures and 413 (56%) of 740 bloodstream infections (see appendix for pathogen types).

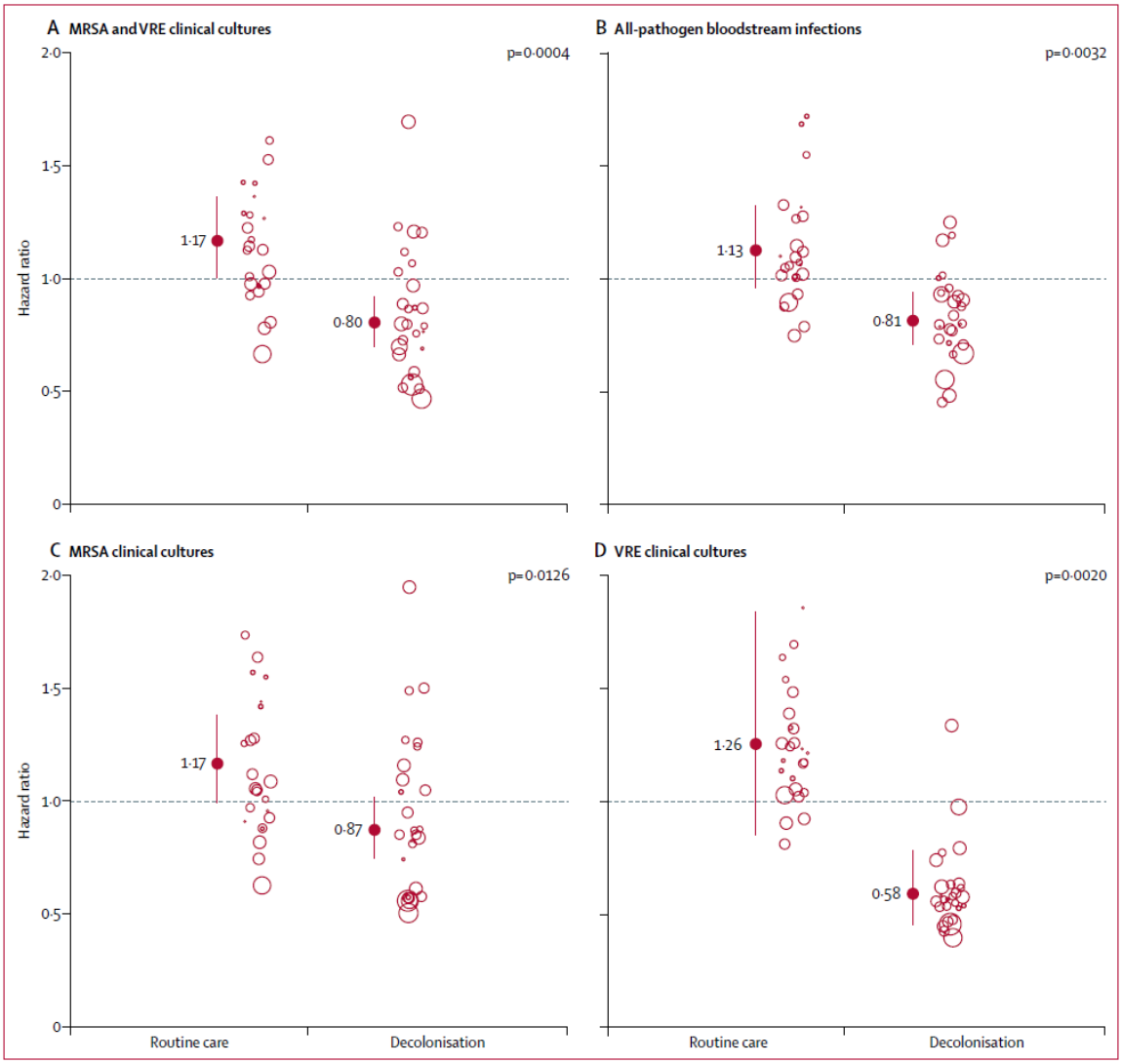

Figure 3: Outcomes in patients with medical devices
Effect of trial interventions on trial outcomes in the post-hoc subpopulation of patients with medical devices. Group-specific hazard ratios and confidence intervals from proportional hazards models (unadjusted, intention to treat) accounting for clustering by hospitals are shown for clinical cultures of MRSA or VRE (A), all-pathogen bloodstream infections (B), MRSA clinical cultures only (3C), and VRE clinical cultures only (D). Results remained significant after adjusting for multiple comparisons. Bubble plots of hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown adjacent to group-specific hazard ratios and confidence intervals. The size of the bubble reflects the relative number of patients contributing data to the subpopulation.

Participating hospitals reported 196 quality improvement interventions to trial investigators. Of these, 129 (66%) were unrelated to the trial while 67 (34%) directly competed with trial outcomes. Hospitals chose not to implement 64 (96%) of the 67 competing quality improvement interventions. Three hospitals dropped from the trial to

pursue the remaining three conflicting interventions. Additionally, HCA released guidance to all hospitals in the health system to initiate universal ICU decolonisation with daily chlorhexidine and nasal mupirocin three months before the start of the baseline period. Results from a sensitivity analysis restricted to patients without a preceding ICU stay prior to entering a participating unit were similar to results from the full trial population.

There were 25 (<1%) adverse events, all involving chlorhexidine, among 183 013 patients in units assigned to chlorhexidine. All were associated with mild pruritus or rash, and all resolved rapidly upon discontinuation. There were no reported adverse events among 2908 patients with a history of MRSA in units assigned to receive mupirocin.

Discussion

There has been widespread adoption of chlorhexidine bathing with or without nasal decolonisation in ICUs across the USA and other countries, in response to cluster-randomised trials[24–27] showing marked reductions in central line-associated bloodstream infections and all-cause bloodstream infections, and reductions in MRSA carriage and transmission. The success of this strategy in ICUs has raised questions about whether the benefit could be extended to other populations, such as non-critically ill hospitalised patients, post-discharge patients, or patients in nursing homes.[28–30]

The ABATE Infection trial found that universal chlorhexidine bathing for all patients outside the ICU plus mupirocin for MRSA carriers did not significantly reduce clinical cultures with multidrug-resistant organisms or all-cause bloodstream infections compared with routine care. This trial was powered to detect a 20% difference in these outcomes; instead, we found an 8% reduction in MRSA or VRE clinical cultures and a 6% reduction in all-cause bloodstream infections. These results were neither significant nor clinically meaningful for a broad-based intervention strategy.

Our trial highlights the importance of having a control group, since both study groups showed significant improvement over baseline values for the primary outcome. The reason for this improvement is not known, since initiation of new infection prevention efforts was closely monitored. We did, however, allow and expect hospitals to organise campaigns to improve adherence to existing best practice. It is possible that the routine care group was more adept at ensuring best practice and invested more effort into such improvement campaigns because they did not have to adopt a new intervention, but this would only affirm that universal chlorhexidine bathing and targeted nasal mupirocin for MRSA carriers does not provide improvement over current best practices for the general non-critical-care patient population.

Because universal decolonisation has been established as best practice in ICU patients,[7–12] the absence of an effect in general medical and surgical patients merits discussion. One possible explanation is that patients in non-critical-care units often take their own baths and showers, and the application of chlorhexidine might be less robust than during fully-assisted ICU care. Nevertheless, we note that nearly 80% of patients who used chlorhexidine used disposable cloths for bathing, which generally implies some level of staff assistance and higher residual concentrations of chlorhexidine on the skin.[31] Furthermore, in comparison to ICU patients, general inpatients have fewer medical devices, are less likely to undergo invasive procedures, are better able to maintain self-

care and personal hygiene, and therefore have a lesser degree of modifiable infection risks. Their length of stay in participating units is also short, only a median of 4 days. Longer follow-ups after discharge might have identified more preventable cases. Application of the intervention beyond discharge or a greater adherence to the protocol could have also provided greater protection. Nevertheless, if we account for the fact that we did not require bathing on the discharge day, the 71% chlorhexidine adherence reflected a robust adoption across many facilities, especially when checklists for appropriate body application and cleansing of medical devices were being applied. In our post-hoc analysis we identified a high-risk subgroup of patients with medical devices (including central lines, midline catheters, and lumbar drains) who significantly benefited from the intervention; in these patients, decolonisation with chlorhexidine decreased allcause bacteraemia by 32% and MRSA or VRE clinical cultures by 37%. This reduction is even more meaningful considering patients with medical devices only represented approximately 10% of the total study population. The mechanism of decolonisation has been well established for chlorhexidine. It reduces body surface bioburden of potentially pathogenic microbes and has strong biological plausibility to reduce infection in the setting of a break in skin integrity due to medical devices.[31–34] Application of chlorhexidine before central line insertion, during dressing changes, and for routine bathing in ICUs has been shown to be superior to other agents and is now established as best practice.[2,3,8,11] Our observations of the benefit of decolonisation in noncritically ill patients with devices is consistent with these ICU findings related to central line-associated bloodstream infections.[8,11,35] In fact, some US hospitals adopted chlorhexidine bathing in all patients with central lines when guidance from national societies recommended this strategy in ICUs only.[35] It should be noted, however, that the benefit reported for patients with devices in the ABATE Infection trial was in the context of a strategy that provided chlorhexidine bathing to all patients. Thus, it is not known whether targeting chlorhexidine bathing and nasal decolonisation only to patients with devices would achieve the same reduction in MRSA, VRE, and all-cause bloodstream infections as observed in the ABATE Infection trial. While the majority of that reduction was likely caused by direct application of these products to patients' skin, it has been shown that chlorhexidine reduces shedding of body surface bacteria into the environment and onto the hands of health-care workers.[36,37] We cannot estimate the proportion of benefit that might have been gained through this indirect type of protection. Additionally, this benefit was achieved with a real-world pragmatic rollout of this intervention in community hospitals with no research staff on-site. Thus, the benefit seen in this population is probably generalisable to other hospitals.

We did not find a significant reduction in MRSA and VRE clinical cultures or bloodstream infection among patients in oncology units. However, this assessment was limited to only seven units, and oncology patients, who often have central lines, contributed to the benefit found in those with medical devices. Larger, more dedicated oncology assessments might be necessary to disentangle whether chlorhexidine exerts a benefit among immunocompromised patients independent of the protection applied to those with medical devices.

This trial has several limitations. Firstly, the study population consisted of patients in general medical and surgical units in community hospitals, where less than

3% had a known history of MRSA or VRE. A population with a higher prevalence or risk of multidrug-resistant organisms or infection could have yielded a different outcome. Secondly, although we have daily nursing documentation of whether chlorhexidine bathing or showering occurred, we have less assurance of the quality of chlorhexidine application to the skin, because we only required direct observation of the quality of bathing three times per unit per 3-month period during the trial. Compared with ICUs, where decolonization has been highly effective in reducing multidrug-resistant organisms and all-cause bloodstream infections, bathing in non-critical-care units is commonly done by nursing assistants rather than nurses. Additionally, patients often opt for their own application of disposable bathing cloths and soap in showers, and thus the quality of application to the skin is likely highly variable. Lastly, the benefit found in the subpopulation of patients with medical devices was a post-hoc analysis and the trial was not originally designed or powered for this evaluation. Any application of chlorhexidine to this or other subpopulations warrants periodic assessment for the emergence of antiseptic resistance over time.

In conclusion, universal daily chlorhexidine bathing plus nasal decolonisation for MRSA carriers does not reduce MRSA or VRE clinical cultures and all-cause bloodstream infections in patients in the general non-ICU population.

Contributors

SSH contributed to study design, study conduct, data analysis, data interpretation, and manuscript drafting. ES, JM, MKH, and RAW contributed to study conduct, data interpretation, and manuscript review. KK contributed to study design, data analysis, data interpretation, analytic plan drafting, and manuscript review. JH, LH, and AG contributed to study conduct, data collection, and manuscript review. TRA contributed to data analysis, data interpretation, and manuscript review. KH, LS, REK, JL, MHC, JAJ, and JBP contributed to study conduct and manuscript review. CS-S, TF, LP, and JS-P contributed to data collection and manuscript review. MVM contributed to data analysis and manuscript review. RP contributed to study design, study conduct, data interpretation, and manuscript review.

Declaration of interests

Sage Products and Mölnlycke contributed antiseptic chlorhexidine product to this trial. Investigators are also taking part in other studies in which participating health-care facilities receive antiseptic products from Sage Products (Stryker) (KK, LH, MHC, MKH, RAW, SSH), 3M (LH, SSH), Clorox (CS-S, ES, JH, JM, JS-P, KH, KK, LH, LS, MHC, MKH, RAW, RP, SSH, TRA), Xttrium (LH, SSH), and Medline (CS-S, ES, JH, JM, JS-P, KH, KK, LH, LS, MHC, MKH, RAW, RP, SSH, TRA). MKH, MHC, LS, KH, and RP received investigator-initiated grant funds from Clorox. All other authors declare no competing interests.

Data sharing

The ABATE Infection trial dataset involves data on over half a million patients. Data sharing requests will be addressed through a supervised data enclave,[38] which will be

maintained behind HCA's firewall on HCA servers for 3 years after the primary publication date. Requests are subject to approval based on planned use of the data, protection of privacy, and scope consistent with the outcomes of the ABATE Infection trial. Only aggregate data (eg, counts, distributions) will be returned. No individual patient-level results will be released. A processing fee will be assessed to cover this service. Request forms are available.

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For the ABATE Infection trial patient bathing video see https://vimeo.com/164608558

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